



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 401/06, 403/06, 409/06 C07D 413/06, A61K 31/40 A61K 31/38, 31/41	A1	(11) International Publication Number: WO 93/07141 (43) International Publication Date: 15 April 1993 (15.04.93)
--	----	--

(21) International Application Number: PCT/US92/08611

(22) International Filing Date: 2 October 1992 (02.10.92)

(30) Priority data:

07/776,508	11 October 1991 (11.10.91)	US
07/916,733	20 July 1992 (20.07.92)	US

(60) Parent Applications or Grants

(63) Related by Continuation

US	07/776,508 (CIP)
Filed on	11 October 1991 (11.10.91)
US	07/916,713 (CIP)
Filed on	20 July 1992 (20.07.92)

(71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BENDER, Paul, Elliot [US/US]; 504 Lilac Lane, Cherry Hill, NJ 08003 (US). CHRISTENSEN IV, Siegfried, Benjamin [US/US]; 2216 Race Street, Philadelphia, PA 19103 (US).

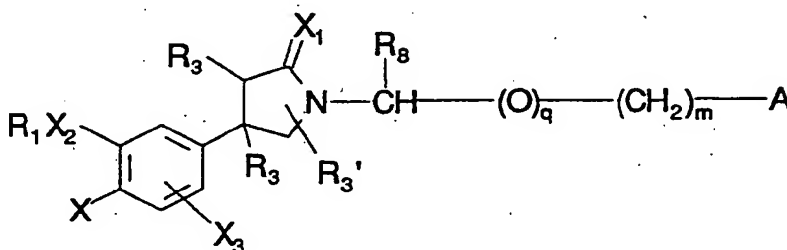
(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S.; UW2220, 709 Swedeland Road, P.O. Box 1538, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published

With international search report.

(54) Title: HETEROCYCLIC 3-PHENYLPYRROLIDIN-2-ONES, THEIR PREPARATION AND USE FOR THE MANUFACTURE OF A MEDICAMENT FOR INHIBITING TUMOR NECROSIS FACTOR PRODUCTION



(I)

(57) Abstract

A compound of formula (I), wherein the substituents are as defined in the claims inhibits the production of tumor necrosis factor (TNF).

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SK	Slovak Republic
CI	Côte d'Ivoire	LK	Sri Lanka	SN	Senegal
CM	Cameroon	LU	Luxembourg	SU	Soviet Union
CS	Czechoslovakia	MC	Monaco	TD	Chad
CZ	Czech Republic	MG	Madagascar	TG	Togo
DE	Germany	ML	Mali	UA	Ukraine
DK	Denmark	MN	Mongolia	US	United States of America
ES	Spain			VN	Viet Nam
FI	Finland				

HETEROCYCLIC 3-PHENYLPYRROLIDIN-2-ONES, THEIR PREPARATION AND USE FOR THE MANUFACTURE OF A MEDICAMENT FOR INHIBITING TUMOR NECROSIS FACTOR PRODUCTION

Field of Invention

5 The present invention relates to novel heterocyclic pyrrolidinones, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

10 Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

 It is now understood that the symptoms of chronic asthma are the
15 manifestations of three distinct processes: 1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperreactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987. The agents currently available (β -adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none
20 of them modify all three phases of asthma and nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

 Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of disease. Thus, it
25 seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

 One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-
30 monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs (Robison et al., Cyclic AMP Academic Press, New York, pgs. 17-47, 1971; Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, pgs. 17-29, 1973). When the appropriate agonist binds to specific cell surface receptors,
35 adenylate cyclase is activated which converts Mg^{2+} -ATP to cAMP at an accelerated rate. The actions of cAMP are terminated by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-AMP, an inactive metabolite.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit PDE should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cyclic AMP breakdown in airway smooth muscle and inflammatory cells. Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd. (1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E₂ and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

TNF has been implicated in various roles with the human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). It has now been discovered that monokines, specifically TNF, are implicated in the infection of T lymphocytes with HIV by playing a role in maintaining T lymphocyte activation. Furthermore, once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. It has also been discovered that monokines, specifically TNF, are implicated in activated T cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., *The Immunopathogenesis of HIV Infection, Advances in Immunology*, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., *Proc. Natl. Acad. Sci.*, 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

It has now been discovered that monokines are implicated in certain disease-associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

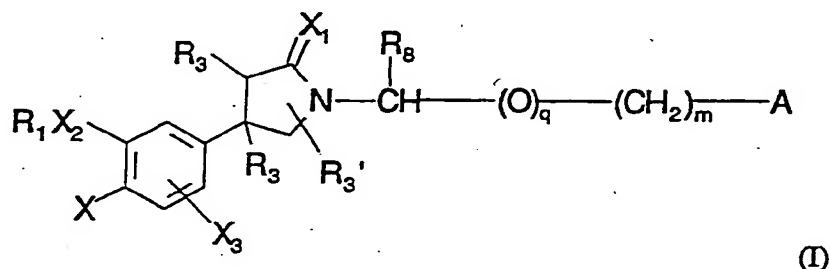
TNF is also associated with yeast and fungal infections. Specifically *Candida Albicans* has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., *Infection and Immunity*, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., *Journal of Infectious Diseases*, Vol. 164, p. 389-95 (1991). See also Wasan et al., *Antimicrobial Agents and Chemotherapy*, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., *Journal of Infectious Diseases*, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

5

Summary of the Invention

The compounds of this invention are illustrated by the formula (I)



10 wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cycloalkyl unsubstituted or substituted by 1 to 3 methyl groups or an ethyl group; C_{4-6} cycloalkenyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl, $-(CR_{14}R_{14})_n C(O)O-(CR_{14}R_{14})_m R_{10}$, $-(CR_{14}R_{14})_n C(O)O-(CR_{14}R_{14})_r R_{11}$, $-(CR_{14}R_{14})_x OH$, $-(CR_{14}R_{14})_s O(CR_{14}R_{14})_m R_{10}$, $-(CR_{14}R_{14})_s O(CR_{14}R_{14})_r R_{11}$, $-(CR_{14}R_{14})_n (C(O)NR_{14})-(CR_{14}R_{14})_m R_{10}$, $(CR_{14}R_{14})_n (C(O)NR_{14})-(CR_{14}R_{14})_r R_{11}$, $-(CR_{14}R_{14})_y R_{11}$ or $-(CR_{14}R_{14})_z R_{10}$;

X_1 is O or S;

X_2 is O or NR_{14} ;

20 X_3 is hydrogen or X;

X is YR_2 , halogen, nitro, $NR_{14}R_{14}$ or formamide;

Y is O or $S(O)_m$;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 5 fluorines;

25 R_3 is independently hydrogen, halogen, CN, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, cyclopropyl unsubstituted or substituted by R_9 , OR_5 , $-CH_2OR_5$, $-NR_5R_{16}$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$, $-CH=CR_9R_9$, $-C\equiv CR_9$, or $-C(Z)H$;

R_3' is hydrogen, halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, cyclopropyl unsubstituted or substituted by R_9 , $-CN$, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or $-C(Z)H$;

30 A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl) or (4 or 5-thiazolyl) all of which may be unsubstituted or substituted by one or more: Br, F, Cl, NR_5R_{16} , NR_6R_{16} ,

NO₂, -COR₇, -S(O)_mR₁₂, CN, OR₅, -OC(O)NR₅R₁₆, (1- or 1-(R₅)-2-imidazolyl),
 -C(NR₁₆)NR₅R₁₆, -C(NR₅)SR₁₂, -OC(O)R₅, -C(NCN)NR₅R₁₆, -C(S)NR₅R₁₆,
 -NR₁₆C(O)R₁₅, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R₅
 and R₁₆ are as NR₅R₁₆ they may together with the nitrogen form a 5 to 7
 5 membered ring optionally containing at least one additional heteroatom selected
 from O, N or S; or A is SR₁₂;

R₅ is independently hydrogen or C₁₋₄alkyl, unsubstituted or substituted by
 one to three fluorines;

R₆ is R₅, -C(O)R₅, -C(O)C(O)R₇, -C(O)NR₅R₁₆, -S(O)_mR₁₂,
 10 -C(NCN)SR₁₂, -C(NCN)NR₅R₁₆, -C(NCN)R₁₂, -C(NR₁₆)R₁₂ or -C(NR₁₆)SR₁₂;

R₇ is OR₅, -NR₅R₁₆ or R₁₂;

R₈ is hydrogen, C(O)R₇, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4-
 or 5-triazolyl-[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl),
 (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-
 15 thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-
 thiazolidinyl) or (2-, 4-, or 5-imidazolidinyl), wherein each of the heterocyclic ring
 systems may be optionally substituted by one or more R₁₄ groups;

R₉ is hydrogen, F or R₁₂;

R₁₀ is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC₁₋₃
 20 alkyl, halo substituted aryloxyC₁₋₃alkyl, indanyl, indenyl, C₇₋₁₁ polycycloalkyl,
 furanyl, pyranal, thienyl, thiopyranal, (3- or 4-tetrahydrothiopyranal), 3-
 tetrahydrofuranal, 3-tetrahydrothienyl, (3- or 4-tetrahydrothiopyranal), C₃₋₆ cycloalkyl
 or a C₄₋₆cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl
 and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl
 25 groups or one ethyl group;

R₁₁ is 2-tetrahydrothiopyranal or 2-tetrahydrothiopyranal, 2-tetrahydrofuranal
 or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one
 ethyl group;

R₁₂ is C₁₋₄alkyl unsubstituted or substituted by one to three fluorines;

30 R₁₄ is independently hydrogen or a C₁₋₂alkyl unsubstituted or substituted by
 fluorine;

R₁₅ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl,
 imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl,
 morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of the heterocyclics may
 35 be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

R₁₆ is OR₅ or R₅;

Z is O, NR₁₂, NOR₅, NCN, C(-CN)₂, CR₅NO₂, CR₅C(O)OR₅,
 CR₅C(O)NR₅R₅, C(-CN)NO₂, C(-CN)C(O)OR₁₂ or C(-CN)C(O)NR₅R₅;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

5 s is an integer from 2 to 4;

x is an integer from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

or a pharmaceutically acceptable salt thereof;

10 provided that m is 2 when R₁₀ is OH in $-(CR_{14}R_{14})_n-C(O)O-$

$(CR_{14}R_{14})_mR_{10}$, $-(CR_{14}R_{14})_n(C(O)NR_{14})(CR_{14}R_{14})_mR_{10}$ or

$C(R_{14}R_{14})_sO(CR_{14}R_{14})_mR_{10}$, and further provided that z is 2 to 6 when R₁₀ is OH in $-(CR_{14}R_{14})_zR_{10}$, and further provided that m is 1 or 2 when A is SR₁₂.

In a second aspect, this invention relates to a pharmaceutical composition
15 containing a compound of formula I in admixture with a pharmaceutically excipient.

This invention further constitutes a method of inhibiting phosphodiesterase IV in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

This invention further constitutes a method of inhibiting the production of
20 TNF in an animal, including humans, which comprises administering to an animal in need thereof, an effective amount of a compound of Formula (I).

Detailed Description of the Invention

Phosphodiesterase IV inhibitors are useful in the treatment of a variety of
25 allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In
30 addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, (Kidney Int. 37:362, 1990; Kidney Int. 35:494, 1989) and central nervous system disorders such as depression and multi-infarct dementia.

These compounds can also be used to treat a human afflicted with a human
immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease
35 state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically administering an effective amount of a compound of Formula I.

5 The compounds of the present invention are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza,
10 adenovirus and the Herpes group of viruses, such as, Herpes Zoster and Herpes Simplex.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo. A preferred disease state for treatment is
15 fungal meningitis. Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles,
20 such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The preferred organism for treatment is the *Candida* organism. The
25 compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in
30 need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Also included in this invention are pharmaceutically acceptable salt complexes of the compounds of this invention which can form salts.

35 All defined alkyl groups can be straight or branched.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present

invention. The term "halogen" is used to mean chloro, fluoro, bromo or iodo. Alkyl groups may be substituted by one or more halogens up to being perhalogenated.

By the term "cycloalkyl" as used herein is meant to include groups of 3-6 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

5 By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

Examples of C₇₋₁₁ polycycloalkyl are bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo [5.2.1.0^{2,6}]decyl, etc., additional
10 examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R₅ and R₁₆ in the moiety -NR₅R₁₆ together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but
15 are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, or pyrrolyl ring.

The invention further provides for the novel pharmaceutical compositions of the compounds of Formula I.

The invention provides a method of inhibiting PDE IV which comprises
20 administering to a subject in need thereof, a compound of Formula (I).

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

The invention also provides a method for the treatment of asthma which
25 comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

The compounds of Formula (I) are useful in treating, prophylactically or therapeutically, disease states in humans which are exacerbated or caused by excessive or unregulated TNF production.

30 Therefore, the present invention also provides a method for the inhibition of the production of tumor necrosis factor (TNF) in an animal in need thereof, including humans, which comprises administering to the animal in need of such treatment an effective amount of a compound of Formula I.

By the term "inhibiting the production of TNF" is meant

35 a) a decrease of excessive in vivo TNF levels in a human to normal levels or below normal levels by inhibition of the in vivo release of TNF by all cells, including but not limited to monocytes or macrophages;

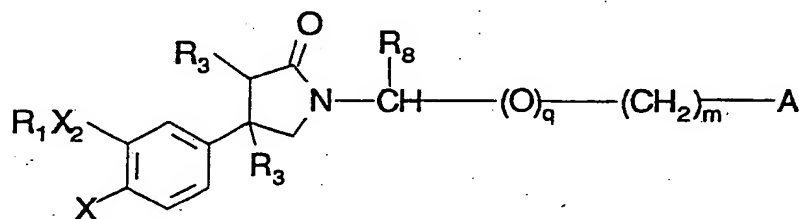
b) a down regulation, at the translational or transcription level, of excessive in vivo TNF levels in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

5 By the term "TNF mediated disease states" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action is exacerbated or which is secreted in response to TNF, would therefore be
10 considered a disease state mediated by TNF.

By the term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them.
15 For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and b-lymphocytes. Lymphokines are generally referred to as being
20 produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF α) and Tumor Necrosis Factor beta (TNF β).

A preferred subgroup of Formula (I) is Formula (Ia):



(Ia)

wherein:

R_1 is phenyl, benzyl or C_{1-2} alkyl unsubstituted or substituted by 1 or more fluorines; C_{4-6} cycloalkyl, CH_2 -cyclopentyl, CH_2 -cyclopropyl, C_{7-11}
30 polycycloalkyl, 3-tetrahydrofuranyl, cyclopentenyl, $-(\text{CH}_2)_n\text{C}(\text{O})-\text{O}-(\text{CH}_2)_m\text{CH}_3$, $-(\text{CH}_2)_2-4\text{OH}$, $-(\text{CH}_2)_5\text{O}(\text{CH}_2)_m-\text{CH}_3$, $-(\text{CH}_2)_n-(\text{C}(\text{O})\text{NR}_{14})-(\text{CH}_2)_m-\text{CH}_3$, all of which may be substituted by 1 to 3 methyl groups or one ethyl group;

s is 2 to 4;

m is 0 to 2;

n is 1 - 3;

X is YR₂, halogen, nitro, amine, C₁₋₂dialkylamine, C₁₋₂monoalkylamine or formamide;

Y is O or S(O)_m;

5 R₂ is -CH₃ or -CH₂CH₃, each may be unsubstituted or substituted by 1 to 4 fluorines;

R₃ is independently hydrogen, CF₂H, CH₂F, -CH₂OR₅, C(O)OR₅, C(O)NR₅R₅, C(O)H, C(NOR₅)H, CH₃, CN, F, OH, -C≡CR₉ or CF₃;

q is 0 or 1;

10 A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1- or 2-imidazolyl), (2- or 3-thienyl) or (4- or 5-thiazolyl), all of which may be unsubstituted or substituted by one or more: Br, F, Cl, -NR₅R₆, NR₅R₁₆, NR₆R₁₆, NO₂, -COR₇, -S(O)_mR₁₂, CN, OR₅, -OC(O)NR₅R₁₆, (1- or 2-imidazolyl), -C(NR₁₆)NR₅R₁₆, -C(NR₅)SR₁₂, -OC(O)R₅, -C(NCN)NR₅R₁₆, -C(S)NR₅R₁₆, -NR₁₆C(O)R₁₅,
15 oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R₅ and R₁₆ are as NR₅R₁₆ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR₁₂;

20 R₅ is independently hydrogen or C₁₋₄alkyl, unsubstituted or substituted by one to three fluorines;

R₆ is R₅, -C(O)R₅, -C(O)C(O)R₇, -C(O)NR₅R₁₆, -S(O)_mR₁₂, -C(NCN)S(R₁₂) or -C(NCN)NR₅R₁₆;

R₇ is OR₅, NR₅R₁₆ or R₁₂;

R₈ is H or -C(O)R₇;

25 R₉ is R₅;

R₁₂ is C₁₋₄alkyl unsubstituted or substituted by one to three fluorines;

R₁₅ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of the heterocyclics may
30 be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

R₁₆ is OR₅ or R₅; or a pharmaceutically acceptable salt thereof;

Preferred compounds are those in which X₁ and X₂ are oxygen, A is an optionally substituted (2-, 3- or 4-pyridyl), 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl; R₁ is CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl, phenyl,
35 tetrahydrofuran-3-yl, cyclopentenyl, -C₁₋₂alkyl optionally substituted by one or more fluorines, -(CH₂)_nC(O)-O-(CH₂)_mCH₃, -(CH₂)_sO(CH₂)_m-CH₃ or -(CH₂)₂₋₄OH; X is YR₂, Y is O; R₂ is a C₁₋₂alkyl optionally substituted by one or more fluorines; one R₃ is hydrogen and the other R₃ is hydrogen, C≡CR₉, CN, C(Z)H,

CH₂OH, CH₂F, CF₂H, or CF₃; Z is O or NOR₅; R₃ is hydrogen; X₃ is hydrogen; and A is an optionally substituted (2-, 3- or 4-pyridyl), 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl.

More preferred are compounds in which R₁ is C₁₋₂ alkyl substituted by 1 or
 5 more fluorines, CH₂-cyclopropyl, CH₂-cyclopentyl, cyclopentyl or cyclopentenyl; R₂ is methyl or fluoro substituted C₁₋₂ alkyl; R₃ is hydrogen, C≡CH or CN; and A is 2-, 3- or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazole or 4-thiazolyl, each of which may be substituted or unsubstituted by NR₅R₁₆ or NR₅C(O)R₅.

Most preferred are compounds wherein R₁ is cyclopentyl, CF₃, CH₂F,
 10 CHF₂, CF₂CHF₂, CH₂CF₃, CH₂CHF₂, CH₃, CH₂-cyclopentyl, CH₂-cyclopropyl or cyclopentenyl; R₂ is CH₃, CF₃, CHF₂, or CH₂CHF₂; one R₃ is hydrogen and the other R₃ is hydrogen, C≡CH or CN and is in the 4-position.

Especially preferred are the following compounds:

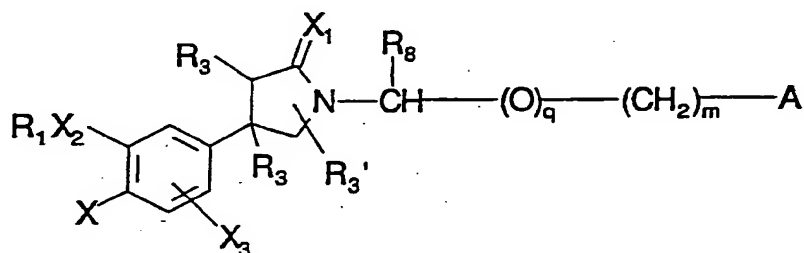
- 15 1-(2-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 1-(3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 1-(4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 20 1-[2-(4-morpholinyl)ethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 1-(2-imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- (S)-(-)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 25 (S)-(-)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- (R)-(+)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 30 (R)-(+)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- (S)-(-)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- (R)-(+)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,
- 35 S-(-)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

R-(+)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, and
4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-methylthioethyl)-2-pyrrolidinone.

5

General Synthesis

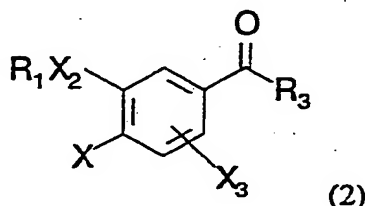
Compounds of the Formula (Ia)



(Ia)

10 can be prepared by a process which comprises:

a) for compounds wherein R₃ is H, R₁₂ or cyclopropyl unsubstituted or substituted by R₉ and X and X₃ are other than S(O)_mR₂ (wherein m = 1 or 2), Br, I, NO₂ or formamide; reacting a compound of the Formula (2)

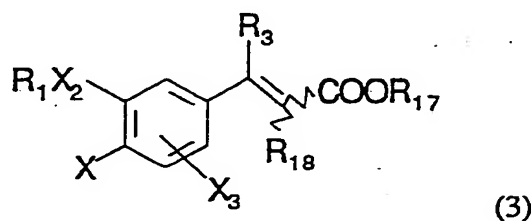


(2)

15

wherein X₂R₁, X and X₃ respectively represent X₂R₁, X and X₃ as defined in relation to Formula (I) or groups convertible to X₂R₁, X and X₃, with an appropriate malonic acid ester derivative, such as dimethyl malonate, in a suitable
20 solvent, such as benzene or toluene, at reflux with or without an appropriate catalyst (e.g., titanium tetrachloride or a tertiary amine base with or without added acid) and/or with azeotropic removal of water under an inert atmosphere, to provide a compound of Formula (3) wherein R₁₇ is an alkyl or aryl group and R₁₈ is COOR₁₇;

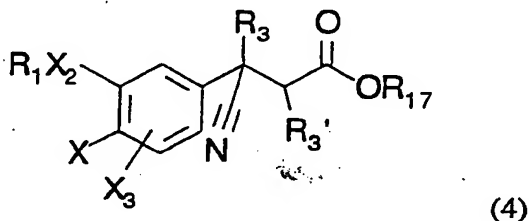
25



(3)

Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetra-alkylammonium cyanide, provides compounds of the Formula (4)

5

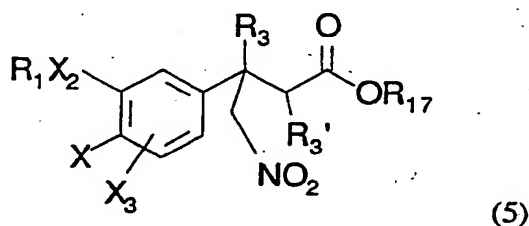


wherein R3' is H or COOR17, typically as a mixture.

Alternatively, reaction of a compound of the Formula (2) with, e.g.,
 10 carboalkoxy- or carboaryloxy-methylene trialkyl- or triarylphosphorane, provides a compound of the Formula (3) wherein R18 is H. Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetraalkylammonium cyanide, also provides compounds of the Formula (4) wherein R3' is H.

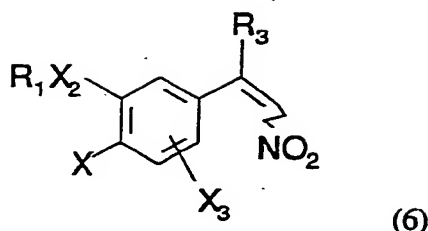
15 Alternatively, reaction of a compound of the Formula (3) wherein R18 is H with the anion of nitromethane generated from an appropriate base or in the presence of an appropriate catalyst, such as alkoxide, a tetraalkylguanidine or a quaternary ammonium halide, in an appropriate solvent, such as an alcohol or nitromethane, provides an ester compound of the Formula (5)

20



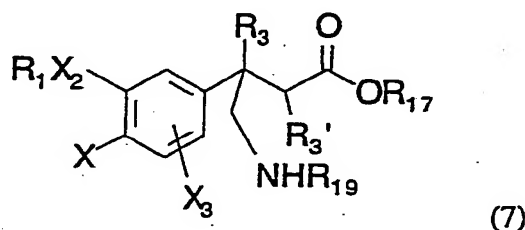
wherein R3' is COOR17, which may be hydrolyzed and decarboxylated to provide a compound of the Formula (5) wherein R3' is H. Similarly, compounds of the
 25 Formula (5) wherein R3' is H, may be derived from first,

1) reaction of a compound of the Formula (2) with nitromethane as described above to provide a compound of the Formula (6)

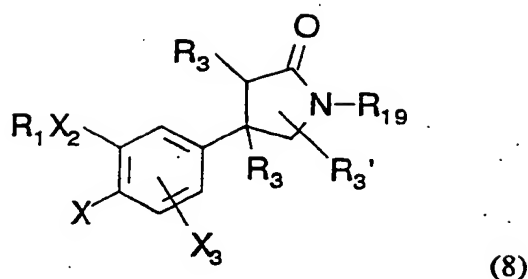


followed by 2) further reaction of a such a compound of the Formula (6) with an alkyl or aryl acetate anion, generated at an appropriate temperature (e.g., -78°C) in an appropriate solvent (e.g., tetrahydrofuran) using an appropriate base (e.g., lithium diisopropylamide or lithium hexamethyldisilazide).

Alternatively, reaction of a compound of the Formula (9) (as described below) wherein R_{20} is H and R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9 with a strong base, followed by reaction with an appropriate alkyl or aryl α -halo carboxylate, such as methyl α -bromoacetate, will also provide a compound of the Formula (4) wherein R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9 . Reduction of the nitrile group of such compounds of the above Formula (4) or of the nitro group of the above similar compounds of the Formula (5) provides compounds of Formula (7)

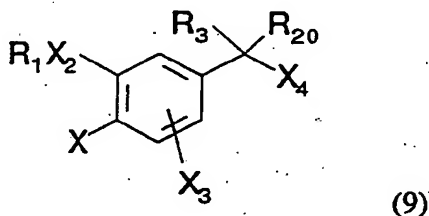


wherein R_{19} is H. Reaction of amines of the Formula (7) wherein R_{19} is H with an aldehyde in a suitable solvent, such as chloroform at reflux temperature, followed by reduction of this imine product with, for example, sodium cyanoborohydride in the presence of an acid in methanol, provides compounds of the Formula (7) wherein R_{19} is $\text{CH}_2(\text{CH}_2)_m\text{A}$; cyclization of such compounds of the Formula (7) then provides the corresponding compounds of Formula (Ia). Alternatively, treatment of compounds of Formula (7) wherein R_{19} is H with or without a catalyst in an appropriate solvent with an appropriate activated alkylating agent, such as a halide, mesylate or tosylate, provides compounds of the Formula (7) wherein R_{19} is $\text{CHR}_8(\text{O})_q(\text{CH}_2)_m\text{A}$, which may be cyclized as above to the corresponding compounds of Formula (Ia). In addition, cyclization of above compounds of the Formula (7) wherein R_{19} is H provides compounds of the Formula (8)



wherein R₁₉ is H; reaction of appropriate compounds of the Formula (8) wherein R₁₉ is H with a strong base, such as sodium hydride, followed by reaction of the generated amide anion with an appropriate activated alkylating agent, such as a halide, mesylate or tosylate, also provides the compounds of the Formula (Ia).

b) for compounds wherein R₃ is CN and X and X₃ are other than S(O)_mR₂ (wherein m is 1 or 2), Br, I, NO₂ or formyl amine, a sequence beginning with reaction of a compound of the Formula (2) wherein R₃ is H with a lithium halide and a silyl halide in an appropriate solvent followed by reduction with an appropriate reductant, such as a siloxane, provides compounds of the Formula (9)



wherein X₄ is chloro or bromo and R₃ and R₂₀ are H; alternatively, reduction of a compound of the Formula (2) wherein R₃ is H with e.g., sodium borohydride in methanol, provides compounds of the Formula (9) wherein X₄ is OH and R₃ and R₂₀ are H, which is reacted with, e.g., phosphorous trichloride, thionyl chloride, phosphorus tribromide, cupric bromide or carbon tetrabromide with triphenyl phosphine, to also provide compounds of the Formula (9) wherein X₄ is chloro or bromo and R₃ and R₂₀ are H. Halide displacement by cyanide then provides compounds of the Formula (9) wherein X₄ is CN and R₃ and R₂₀ are H, which is allowed to react with a strong base, such as a butyl lithium, at reduced temperature under an inert atmosphere and then may be a) treated with, e.g., anhydrous magnesium bromide, and then reacted with, for example, trimethylsilyl isocyanate and appropriate workup, to produce compounds of Formula (9) wherein R₃ is CONH₂, R₂₀ is H and X₄ is CN or b) reacted with, for example, an alkyl or aryl haloformate, such as methyl chloroformate, to produce compounds of the Formula (9) wherein R₃ is COOR₁₇, R₂₀ is H and X₄ is CN; the COOR₁₇ group of such a

compound may be transformed either at this or a later stage to a CONH₂ group by any of the standard techniques known in the art, such as reaction with concentrated ammonium hydroxide.

Alternatively, a compound of the Formula (9) wherein R₃ is COOR₁₇, R₂₀ is H and X₄ is CN may also be obtained by reaction of a compound of the Formula (9) wherein R₃ and R₂₀ are H and X₄ is CN with a metal hydride, such as sodium hydride, in the presence of a dialkyl or diaryl carbonate, such as dimethyl carbonate. Also, such compounds may be obtained by homologation of a compound of the Formula (2) wherein R₃ is H to a compound of the Formula (9) wherein R₃ is COOR₁₇ and X₄ and R₂₀ are H by any number of known processes, such as reaction with methyl methylsulfinylmethyl sulfide and a base, e.g., sodium hydroxide, followed by treatment with, e.g., alcoholic acid. Generation of an anion of such compounds of the Formula (9) with a suitable base, followed by reaction with, e.g., cyanogen chloride or 2-chlorobenzyl thiocyanate, provides compounds of the Formula (9) wherein R₃ is COOR₁₇, R₂₀ is H and X₄ is CN. Generation of an anion from compounds of the Formula (9) wherein R₂₀ is H, X₄ is CN and R₃ is CONH₂ or COOR₁₇ with the appropriate base in an appropriate solvent followed by reaction with an alkyl or aryl α -halo carboxylate provides a compound of Formula (4) wherein R₃ is CONH₂ or COOR₁₇; reduction of the nitrile moiety of such compounds by, for example, hydrogenation with a noble metal or Raney nickel catalyst, provides compounds of the Formula (7) wherein R₁₉ is H and R₃ is CONH₂ or COOR₁₇. The amine moiety of compounds of the Formula (7) wherein R₁₉ is H and R₃ is CONH₂ is then protected to provide a compound of the Formula (7) wherein R₁₉ is a protecting group, such as a t-butyloxycarbonyl group, and R₃ is CONH₂; amide dehydration with, for example, trifluoroacetic anhydride, followed by protecting group removal then provides compounds of the Formula (7) wherein R₁₉ is H and R₃ is CN, which may then be transformed as described above for other compounds of the Formula (7) to the compounds of the Formula (1a) wherein R₃ is CN and X and X₃ are other than S(O)_mR₂ (wherein m = 1 or 2), Br, I, NO₂ or formamide.

c) compounds wherein R₃ of Formula (I) is OR₅ or F and X and X₃ are other than S(O)_mR₂ (wherein m is 1 or 2), Br, I, NO₂ or formamide are prepared employing a sequence beginning with a cyanohydrin with the hydroxyl suitably protected as a silyl ether, an acetal, or an ester such as a t-BOC. Treatment of a compound of the Formula (2) wherein R₃ is H, R₁₂ or cyclopropyl unsubstituted or substituted by R₉ with, for example, a derivative of hydrocyanic acid provides the cyanohydrins of Formula (9) wherein R₃ is H, R₂₀ is OH and X₄ is CN. Subsequent treatment of the Formula (9) compounds with a suitable protecting agent

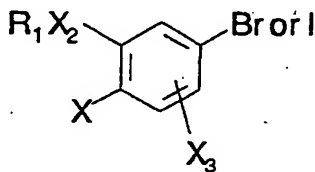
such as trimethylsilyl chloride, di-*t*-butyldicarbonate and a suitable base, or methyl vinyl ether or direct treatment of the Formula (2) compound with trimethylsilylcyanide and a Lewis Acid provides the protected cyanohydrin of Formula (9) in which R₃ is H, R₂₀ is the protected hydroxyl and X₄ is CN. The protected cyanohydrin is treated with a strong hindered base, such as LDA, at reduced temperature under an inert atmosphere followed by reaction with, e.g., a bromoacetic acid ester and appropriate workup to produce a compound of Formula (4) wherein R₃ is the protected hydroxyl and R_{3'} is H. Reduction of the nitrile moiety of such compounds by, for example, hydrogenation with Raney nickel catalyst, provides Formula (7) compounds wherein R₁₉ is H and R₃ is the protected or unprotected hydroxyl. These Formula (7) compounds may be alkylated on nitrogen and cyclized as described above, then treated with diethylaminosulfur trifluoride to provide the Formula (Ia) compounds wherein R₃ is F.

d) compounds of Formula (Ia) wherein R₃ represents the remaining R₃ groups of Formula (Ia) may be derived from the compounds of the Formulas (8) or (Ia) wherein R₃ is CN by protection of the amide and other sensitive functionality, and manipulation of the CN function as, for example, reduction of the R₃ CN moiety to CHO and functional group transformation of the CHO by any of the standard conditions well known in the art.

Some compounds of Formula (Ia) are prepared from other compounds of Formula (Ia) by appropriate manipulation of functional groups present in or as the A, X, X₁, X₂R₁, R₃ or R_{3'} moieties.

Compounds of Formula (Ia) wherein R₃ is CF₃, CHF₂ or CH₂F may be prepared from the corresponding Formula (2) compounds using the methods described above. The formula (2) compounds where R₃ is CF₃ are obtained by the method of Shono et al., J. Org. Chem., Vol. 56, pages 204 (1991) electrochemically from the Formula (2) compounds where R₃ is H.

Formula (2) compounds where R₃ is CF₃ or CF₂H are obtained by treatment of compounds of the Formula (10)



(10)

with a metalling agent at -78°C followed by trifluoroacetic acid or difluoroacetic acid by the method of Nad et al., Izvest, (1959) page 71; Chem. Abstr. vol. 53, No. 14977; and Vol. 53, No. 17933 (1959).

Formula (2) compounds where R₃ is CH₂F are obtained by treatment of the Formula (2) compounds where R₃ is CH₃ according to the method of Rozen et al., Synthesis (6)665, (1985).

For compounds wherein X is S(O)_mR₁₂, and m is 1 or 2 the final compound
5 is made from the -SR₁₂ moiety by oxidizing the intermediate -SR₁₂ product under conditions well known to those skilled in the art, after the appropriate CONH₂ moiety in the synthetic sequence is dehydrated to the cyano moiety. For compounds where X and/or X₃ are Br, I, nitro, amine or formamide, synthesis of these compounds is accomplished by any of the steps described above using a suitably
10 protected amine as X and/or X₃. Such protecting groups are known to those skilled in the art and are readily disclosed in Greene, T., Protective Groups in Organic Synthesis, Wiley Publishers, NY (1981), the contents of which are hereby incorporated by reference. The deprotected amine is then appropriately acylated to the formyl amine moiety, oxidized to the NO₂ moiety, or diazotized and displaced
15 by methods well known to those skilled in the art to produce the desired Br or I moiety.

With appropriate manipulation and protection of any chemical functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the
20 Experimental section. Methods for chiral synthesis of the appropriate compounds of Formula (I) are found in co-pending application No. 07/694,624, which is incorporated by reference herein.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally
25 formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, sublingually, transdermally, rectally, via inhalation or
30 via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil,
35 glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose.

Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg to 100 mg/Kg, and preferably from .01 mg to 30 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. Each dosage unit for intranasal administration or oral inhalation contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I). Each dosage unit for rectal administration contains suitably 0.01 mg to 100 mg of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.001

mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 1200 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit antiinflammatory activity, or if used as a TNF inhibitor, the active ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

The biological activity of the compounds of Formula I as PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula I on PDE IV

I. Isolation of PDE Isozymes

Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (Torphy et al., J. Biol. Chem., 267: 1798-1804 (1992)).

TABLE 1. Characteristics of PDE isozymes.^a

Peak	Isozyme	K _m (mM)	
		cAMP	cGMP
Ia	cGMP-specific	135	4
Ib	Ca ²⁺ /calmodulin-stimulated	50	5
Ic	Ca ²⁺ /calmodulin-stimulated	1	2
III	cGMP-inhibited	0.4	8
IV	Ro 20-1724-inhibited	4	38

^a Data are from Torphy and Cieslinski, *supra*.

^b Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22:1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990. IC₅₀s for compounds of this invention range
5 from 25 nM to 500 μ M.

III. cAMP Accumulation in U-937 Cells

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV
10 inhibition in intact cells, nondifferentiated U-937 cells (approximately 10⁵ cells/reaction tube) were incubated with various concentrations (0.01-100 μ M) of PDE inhibitors for one minute and 1 μ M prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general
15 protocol for this assay is described in Brooker et al., Radioimmunoassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. Data are expressed as both an EC₅₀ for increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC₅₀s for compounds of this invention range from 0.3 μ M to > 10 μ M.

20 Inhibitory Effect of Compounds of Formula (I) on TNF Production

I. Inhibitory Effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes:

The inhibitory effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes may be determined by the protocol as described in
25 Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

II. In vivo activity

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is
30 described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The following examples are given to illustrate the invention. They are not
35 intended to limit the invention in any manner. Reference is made to the claims for what is reserved to the inventors hereunder.

EXAMPLE 1

2-Acetamidopyridine-4-carboxaldehyde

1a) 2-Acetamido-4-picoline To a solution of 2-amino-4-picoline (4.33 g, 40 mmol) in pyridine (50 mL) at 0°C under an argon atmosphere was added dropwise over 15 min, a solution of acetyl chloride (3.3 mL, 46 mmol) in methylene chloride (10 mL). After 0.5 h, the mixture was partitioned between water and methylene chloride, the organic extract was dried over potassium carbonate, filtered and evaporated. Purification by flash chromatography, eluted with 50 % ether/hexanes, provided a white solid : m.p. 99 - 101°C.

1b) 2-Acetamido-4-picoline-1-oxide A solution of 2-acetamido-4-picoline (1.5 g, 10 mmol) and 3-chloroperbenzoic acid (80%, 2.4 g, 11 mmol) in methylene chloride (20 mL) was stirred at room temperature under an argon atmosphere for 18 h. The mixture was treated with solid sodium bicarbonate, poured into water and extracted three times with methylene chloride. The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography, eluted with 5 % methanol/methylene chloride, to provide a white solid: m.p. 138 - 140°C.

1c) 2-Acetamido-4-hydroxymethylpyridine A solution of 2-acetamido-4-picoline-1-oxide (1.56 g, 9.39 mmol) in acetic acid (10 mL) was added dropwise over 0.5 h to refluxing acetic anhydride maintained under an argon atmosphere. After stirring at reflux for 1 h after the addition, the mixture was cooled, diluted with water, neutralized with sodium bicarbonate and extracted five times with ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered and evaporated. The residual oil was dissolved in methanol (10 mL), a solution of sodium methoxide in methanol (25%, 12 mL) was added and the mixture was stirred at room temperature for 1 h. After addition of aqueous sodium chloride, the mixture was extracted five times with ethyl acetate, the organic extract was dried over potassium carbonate and evaporated. The residue was purified by flash chromatography, eluting with 5% methanol/methylene chloride, to provide a white solid: m.p. 130 - 132°C.

1d) 2-Acetamidopyridine-4-carboxaldehyde A solution of 2-acetamido-4-hydroxymethyl-pyridine (645 mg, 3.88 mmol) in pyridine (15 mL) with manganese dioxide (2.36 g, 27.2 mmol) was heated at 105 - 110°C for 1.5 h, then cooled and filtered through Celite, washing well with methylene chloride. The solvents were evaporated and the residue was purified by flash chromatography, eluting with 50% ethyl acetate/hexanes, to provide a white solid: m.p. 139 - 140°C.

EXAMPLE 22-Acetamidopyridine-5-carboxaldehyde

2a) Methyl 6-aminonicotinate A solution of 6-aminonicotinic acid (3.31 g, 24 mmol) in methanol (50 mL) and concentrated sulfuric acid (5 mL) under an argon atmosphere was heated at reflux for 16 h. After cooling, the mixture was basified with potassium carbonate, filtered and evaporated. The residue was partitioned between 5% aqueous sodium carbonate and methylene chloride containing 5% methanol, the organic extract was dried over potassium carbonate, filtered and evaporated to provide a white solid : m.p. 158 - 159°C.

2b) 2-Amino-5-hydroxymethylpyridine Methyl 6-aminonicotinate (3.52 g, 23.1 mmol) was added in twelve portions over the course of 1 h to a suspension of lithium aluminium hydride (1.76 g, 46.2 mmol) in tetrahydrofuran (100 mL) at 0°C under an argon atmosphere and the mixture was stirred at room temperature for 18 h. An additional quantity of lithium aluminium hydride (0.88 g) was added slowly. The mixture was stirred for 6 h. The mixture was cooled to -78°C and water (2.5 mL), aqueous sodium hydroxide (15%, 2.5 mL) and water (7.5 mL) were added in sequence. The mixture was brought to room temperature, and filtered through Celite. The solid was washed well with 10% methanol/methylene chloride, and the filtrate evaporated. Water was added to the residue and it was extracted several times with 10% methanol/methylene chloride. The organic extracts were dried over potassium carbonate, filtered and evaporated. The residue was purified by flash chromatography, eluting with 7.5% methanol/methylene chloride, to provide a white solid : m.p. 117 - 119°C.

2c) 2-Acetamido-5-hydroxymethylpyridine To a solution of 2-amino-5-hydroxymethyl-pyridine (1.09 g, 8.9 mmol) in pyridine (2.15 mL) and methylene chloride (10 mL) at 0°C under an argon atmosphere was added dropwise over 30 min a solution of acetyl chloride (1.6 mL, 22.2 mmol) in methylene chloride (10 mL). After 0.5 h, the mixture was treated with methanol to homogeneity, applied directly to the column and purified by flash chromatography, eluted with 7.5% methanol/methylene chloride, to provide a white solid (1.24 g, 67%): m.p. 85 - 85°C. This solid (1.23g, 5.94 mmol), in methanol (15 mL) was stirred with a solution of sodium methoxide in methanol (25%, 3.25 mL, 14.85 mmol) for 2 h at room temperature under an argon atmosphere. The resultant precipitate was removed by filtration and the filtrate was evaporated. The residue was partitioned between water and 5% methanol/methylene chloride, the organic layer was dried over potassium carbonate, filtered and evaporated to a white solid (845 mg, 86%): m.p. 148 - 150°C.

2d) 2-Acetamidopyridine-5-carboxaldehyde A solution of 2-acetamido-5-hydroxymethyl-pyridine (610 mg, 3.67 mmol) in pyridine (10 mL) was added rapidly to a suspension of pyridinium chlorochromate (1.58 g, 7.34 mmol) in methylene chloride (7 mL) at 0°C under an argon atmosphere. After 0.5 h, ether (50 mL) was added, the mixture was filtered through celite and the filtrate evaporated. The residue was purified by flash chromatography, eluted with 50% ethyl acetate/hexanes, to provide a white solid: m.p. 148 - 149°C.

EXAMPLE 3

10 Methyl (S)-(+)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate

To a solution of (S)-(+)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (152 mg, 0.55 mmol) in dry methylene chloride (2 mL) at room temperature under an argon atmosphere was added triethylamine (0.075 mL, 0.55 mmol), 4-dimethylaminopyridine (67 mg, 0.55 mmol) and di-t-butyldicarbonate (242 mg, 1.09 mmol). After stirring for 1.5 h, the mixture was purified by flash chromatography, eluted with 5% methanol/methylene chloride, to produce a white solid: m.p. 87-89°C. This solid in dry methanol (2 mL) at room temperature under an argon atmosphere was treated with 25% sodium methoxide/methanol (0.125 mL, 0.6 mmol). After stirring for 0.5 h, the mixture was poured into saturated aqueous sodium chloride and extracted three times with methylene chloride. The extract was dried over magnesium sulfate, filtered and evaporated to a white solid: m.p. 73-75°C. $[\alpha]_D^{25}$ (1.14, methanol) = +0.79.

EXAMPLE 4

25 Methyl (R)-(-)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate

To a solution of (R)-(-)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (150 mg, 0.55 mmol) in dry methylene chloride (20 mL) at room temperature under an argon atmosphere was added triethylamine (0.075 mL, 0.55 mmol), 4-dimethylaminopyridine (66 mg, 0.55 mmol) and di-t-butyldicarbonate (245 mg, 1.09 mmol). After stirring for 1.5 h, the mixture was purified by flash chromatography, eluting with 5% methanol/methylene chloride, to produce a white solid: m.p. 83-84°C. This solid in dry methanol (2 mL) at room temperature under an argon atmosphere was treated with 25% sodium methoxide/methanol (0.125 mL, 0.6 mmol). After stirring for 0.5 h, the mixture was poured into saturated aqueous sodium chloride, then extracted three times with methylene chloride. The extract

was dried over magnesium sulfate, filtered and evaporated to a white solid (215 mg, 97%): m.p. 75-77°C. $[\alpha]_D^{25}$ (1.07, methanol) = -0.65.

EXAMPLE 5

5 (R)-1-(2-Acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (R)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (239 mg, 0.59 mmol) in chloroform (2.5 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at
10 room temperature for 3.5h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-4-thiazolecarboxaldehyde (105 mg, 0.60 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 3.5h and then evaporated.
15 The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (115 mg, 1.8 mmol) in methanol (1.0 mL) was added followed by the dropwise addition of 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (4.2 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and
20 partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 3 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed three times with water and dried over
25 potassium carbonate. Purification by flash chromatography, eluting with 2% methanol/methylene chloride, provided a yellow material: m.p. 71 - 75°C. Analysis Calc. for C₂₂H₂₇N₃O₄S·1/2 H₂O: C 60.25, H 6.44, N 9.58; found: C 60.32, H 6.62, N 9.31.

30

EXAMPLE 6

(S)-1-(2-Acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (S)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (249 mg, 0.61 mmol) in chloroform (2.5 mL) at 0°C under
35 an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-4-thiazolecarboxaldehyde (104 mg, 0.61 mmol) was added and the

mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 4 h and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (114 mg, 1.8 mmol) in methanol (1.0 mL) was added followed by the dropwise addition of 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (4.25 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed three times with water and dried over potassium carbonate. Purification by successive flash chromatography, eluting first with 2.5% methanol/methylene chloride followed by 1.5% methanol/methylene chloride, provided a sticky yellow material. Analysis Calc. for C₂₂H₂₇N₃O₄S·1/10 H₂O: C 61.26, H 6.36, N 9.74; found : C 61.11, H 6.38, N 9.47.

EXAMPLE 7

1-(2-Pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (275 mg, 1.0 mmol) in dry dimethylformamide (5 mL) was treated with sodium hydride (35 mg, 1.17 mmol of an 80% dispersion) and stirred under an argon atmosphere. After 15 min, 15-crown-5 ether (200mL, 1.007 mmol) was added and the reaction stirred at room temperature for an additional two hours. 2-Picolyl chloride (175 mg, 1.37 mmol) was added. After stirring at room temperature for 16 hours, water was added to the reaction mixture and it was extracted with 9:1 ether/methylene chloride. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield a yellow oil, which was purified by flash chromatography, eluting with 95:5 ether/methanol. The resulting oil was dissolved in 9:1 ether/methylene chloride and treated with 0.75 mL of 1.0 M hydrochloric acid in ether to provide the solid hydrochloride salt, which was recrystallized from acetonitrile and ether: m.p. 132-133°C. Analysis Calc. for C₂₂H₂₆N₂O₃·HCl: C 65.58, H 6.75, N 6.95; found : C 65.73, H 6.94, N 7.01.

EXAMPLE 81-(3-Pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone
hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (275
5 mg, 1.0 mmol) in dry dimethylformamide (5 mL) was treated with sodium hydride
(35 mg, 1.17 mmol of an 80% dispersion) and stirred under an argon atmosphere.
After 15 min, 15-crown-5 ether (200 mL, 1.007 mmol) was added and the reaction
stirred at room temperature for an additional 2.5 hours. 3-Picolyl chloride (175 mg,
1.37 mmol) was added. After stirring at room temperature for 72 hours, water was
10 added to the reaction mixture and it was extracted with 9:1 ether/methylene chloride.
The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to
yield a yellow oil, which was purified by flash chromatography, eluting with 94:6
ether/methanol. The resulting oil was dissolved in 9:1 ether/methylene chloride and
treated with 0.85 mL of 1.0 M hydrochloric acid in ether to provide the solid
15 hydrochloride salt, which was recrystallized from acetonitrile and ether): m.p. 160-
162°C. Analysis Calc. for C₂₂H₂₆N₂O₃·HCl: C 65.58, H 6.75, N 6.95; found :
C 65.83, H 6.88, N 7.05.

EXAMPLE 9

20 1-(4-Pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone
hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (275
mg, 1.0 mmol) in dry dimethylformamide (5 mL) was treated with sodium hydride
(35 mg, 1.17 mmol of an 80% dispersion) and stirred under an argon atmosphere.
25 After 15 min, 15-crown-5 ether (200mL, 1.007 mmol) was added and the reaction
stirred at room temperature for an additional two hours. 4-Picolyl chloride (175 mg,
1.37 mmol) was added. After stirring at room temperature for 16 hours, water was
added to the reaction mixture and it was extracted with 9:1 ether/methylene chloride.
The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to
30 yield a yellow oil, which was purified by flash chromatography, eluted with 94:6
ether/methanol. The resulting oil was dissolved in 9:1 ether/methylene chloride and
treated with 0.85 mL of 1.0 M hydrochloric acid in ether to provide the solid
hydrochloride salt, which was recrystallized from acetonitrile and ether; m.p. 160-
163°C. Analysis Calc. for C₂₂H₂₆N₂O₃·HCl: C 65.58, H 6.75, N 6.95; found : C
35 65.72, H 6.73, N 7.04.

EXAMPLE 101-[2-(4-Morpholinyl)ethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (200 mg, 0.73 mmol) in dry dimethylformamide (4 mL) was treated with sodium hydride (40 mg, 1.0 mmol of an 60% dispersion) and stirred under an argon atmosphere overnight. 15-crown-5 ether (200 mL, 0.9 mmol) was added to the flask. In a separate flask, 2-chloroethylmorpholine hydrochloride (322 mg, 1.7 mmol) was dissolved in dimethylformamide (1 mL) and treated with sodium hydride (80 mg, 2.0 mmol of a 60% dispersion) to release the free base, and stirred under an argon atmosphere for 1h. The 2-chloroethylmorpholine solution was added to the amidate anion and the reaction stirred for 48h. Ice-water was added to the reaction mixture and it was extracted with ethyl acetate/ether/methylene chloride and washed with water. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield a yellow oil, which was purified by flash chromatography, eluting with 85:15 methylene chloride/acetone adding 0.5-6% methanol. The resulting oil was dissolved in ether/methylene chloride and treated with 0.5 mL of 1.0 M hydrochloric acid in ether to provide the solid hydrochloride salt, which was recrystallized from ethyl acetate: m.p. 159-160°C. Analysis Calc. for C₂₂H₃₂N₂O₄·HCl·1/4H₂O : C 61.53, H 7.86, N 6.52, Cl 8.26; found: C 61.28, H 7.63, N 6.37, Cl 8.10.

EXAMPLE 111-(2-Imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

11a) 1-[2-(1-Benzyl)imidazolymethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (300 mg, 1.09 mmol) in dry dimethylformamide (3.5 mL) was treated with sodium hydride (70 mg, 1.75 mmol of an 60% dispersion) and 15-crown-5 ether (200 mL, 0.9 mmol) and stirred under an argon atmosphere for 5 h. A solution of the 2-chloromethyl-1-benzylimidazole (289 mg, 1.19 mmol) in dimethylformamide (2 mL) was added and stirred under an argon atmosphere for 2h. Ice-water was added to the reaction mixture and it was extracted with ethyl acetate and washed with water. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield an oil, which was purified by flash chromatography, eluting with 3:1 ethyl acetate/petroleum ether and adding 4-6% isopropanol to provide an oil.

11b) 1-(2-Imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-[2-(1-benzyl)imidazolymethyl]-4-(3-cyclopentyloxy-

4-methoxyphenyl)-2-pyrrolidinone (225 mg, 0.5 mmol) and 70% perchloric acid (13 drops) were added to a suspension of 10% palladium on carbon (125 mg) in ethanol (50 mL). The mixture was hydrogenated at 50 psi for 60 h, filtered through celite and evaporated. The residue was partitioned between ethyl acetate and 5% aqueous sodium carbonate and extracted three times. The organic layer was dried (potassium carbonate), evaporated *in vacuo* and purified by flash chromatography, eluting with 3:1 ethyl acetate/hexanes, adding 0-10% methanol to provide an oil and recovered starting material which was subjected to the reaction conditions a second time. The two isolated products were combined and were recrystallized from ethyl acetate/ether: m.p. 76-79°C. Analysis Calc. for $C_{20}H_{25}N_3O_3 \cdot 1/4H_2O$: C 66.73, H 7.14, N 11.67; found: C 66.67, H 7.16, N 11.76.

EXAMPLE 12

(S)-(-)-1-(3-Acetamido-4-pyridylmethyl)-4-(3cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (S)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (251 mg, 0.61 mmol) in chloroform at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted three times with chloroform. 2-Acetamido-4-pyridinecarboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 3.5 h and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (38 mg, 0.61 mmol) in methanol (1.0 mL) was added and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (5 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo* to provide a pale green foam. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water and dried over potassium carbonate. Purification by flash chromatography, eluting with 2.5% methanol/methylene chloride, provided a white solid: 143-145°C.

Analysis Calc. for $C_{24}H_{29}N_3O_4 \cdot 1/4H_2O$: C 67.35, H 6.95, N 9.82; found: C 67.26, H 6.92, N 9.73. $[\alpha]_D^{25}$ (0.86, methanol) = -32.1.

EXAMPLE 13(S)-(-)-1-(4-Acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

5 A solution of methyl (S)-4-*t*-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (215 mg, 0.53 mmol) in chloroform (2.5 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 1.5h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted two times with
10 chloroform. 2-Acetamido-pyridine-5-carboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 4.0 h and then evaporated. The resulting pale orange foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL) under an argon atmosphere. Sodium
15 cyanoborohydride (100.3 mg) was added with methanol (0.5 mL) and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.6 mL) in tetrahydrofuran (5 mL). After 15 min, the mixture was neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl
20 sulfoxide (2 mL) and a trace of sodium cyanide were added. The mixture was stirred for 3.5 hours at 90°C, cooled, diluted with water and extracted twice with ethyl acetate. The organic extract was washed five times with water and dried over potassium carbonate. Purification by flash chromatography, eluting with 2.5% methanol/methylene chloride, provided a white foam: m.p. 73-75°C. Analysis Calc.
25 for C₂₄H₂₉N₃O₄·1/8H₂O: C 67.70, H 6.92, N 9.87; found: C 67.68, H 6.97, N 9.83. $[\alpha]_D^{25}$ (0.80, methanol) = -44.4.

EXAMPLE 14(R)-(+)-1-(3-Acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

30 A solution of methyl (R)-4-*t*-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (250 mg, 0.61 mmol) in chloroform at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with sodium bicarbonate, cold 5%
35 sodium carbonate was added and the mixture was extracted three times with chloroform. 2-Acetamido-pyridine-4-carboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 3.5 h and

then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (38 mg, 0.61 mmol) in methanol (1.0 mL) was added and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (5 mL). The mixture was stirred for one
5 hour under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo* to provide a pale green foam. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled
10 and was extracted twice with ethyl acetate. The organic extract was washed four times with water and dried over potassium carbonate. Purification by flash chromatography, eluting with 2% methanol/methylene chloride, provided a white solid: 143 -144°C.

Analysis Calc. for $C_{24}H_{29}N_3O_4 \cdot 1/4H_2O$: C 67.34, H 6.95, N 9.82; found : C
15 67.27, H 6.88, N 9.73. $[\alpha]_D^{25}$ (0.92, methanol) = +31.4.

EXAMPLE 15

(R)-(+)-1-(4-Acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-
2-pyrrolidinone

20 A solution of methyl (R)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (215 mg, 0.53 mmol) in chloroform (2.5 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 1.5h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted two times with
25 chloroform. 2-Acetamido-pyridine-5-carboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 4.0 h and then evaporated. The resulting pale orange foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1 mL) under an argon atmosphere. Sodium
30 cyanoborohydride (100.3 mg) was added with methanol (0.5 mL) and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.6 mL) in tetrahydrofuran (5 mL). After 45 min, the mixture was neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. The product
35 was treated with dimethyl sulfoxide (2 mL) with a trace of sodium cyanide and stirred at 85-90°C for 4h. The mixture was diluted with water and extracted twice with ethyl acetate. The organic extract was washed five times with water and dried

over potassium carbonate. Purification by flash chromatography, eluting with 2.5% methanol/methylene chloride, provided a white foam: m.p. 75-77°C.

Analysis Calc. for $C_{24}H_{29}N_3O_4 \cdot 1/8H_2O$: C 67.70, H 6.92, N 9.87; found: C 67.52, H 6.89, N 9.89. $[\alpha]_D^{25}$ (0.86, methanol) = +43.7.

5

EXAMPLE 16

(R)-1-(2-Acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (R)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (285 mg, 0.70 mmol) in chloroform (2.5 mL) under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 2.5h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-5-thienylcarboxaldehyde (119 mg, 0.70 mmol) and a small amount of ethyl acetate were added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated. Chloroform was added and this mixture was refluxed for 4 h, stirred at room temperature overnight and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (134 mg, 2.1 mmol) and acetic acid (0.08 mL) were added, the mixture was stirred for two hours under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extracts were dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 1.5 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water, then with brine and dried over potassium carbonate. Purification by successive flash chromatography with 2% methanol/methylene chloride provided a foam. Analysis Calc. for $C_{23}H_{28}N_2O_4S \cdot 0.5 H_2O$: C 63.14, H 6.68, N 6.40; found: C 63.22, H 6.57, N 6.36. $[\alpha]_S(25,D)$ (1.12, methanol) = +32.95.

30

EXAMPLE 17

(S)-1-(2-Acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (S)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (285 mg, 0.70 mmol) in chloroform (2.5 mL) under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-5-

thienylcarboxaldehyde (118 mg, 0.70 mmol) and a small amount of ethyl acetate were added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated. Chloroform was added and this mixture was refluxed for 4 h, stirred at room temperature overnight and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (132 mg, 2.1 mmol) and acetic acid (0.08 mL) were added, the mixture was stirred for two hours under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extracts were dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water, then with brine and dried over potassium carbonate. Purification by successive flash chromatography with 1.75 to 2.5% methanol/methylene chloride provided a foam. Analysis Calc. for C₂₃H₂₈N₂O₄S·0.3 H₂O: C 63.66, H 6.64, N 6.46; found: C 63.66, H 6.58, N 6.36. [α]_D(25,D) (1.18, methanol) = -33.98.

EXAMPLE 18

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2-methylthioethyl)-2-pyrrolidinone.

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.3 g, 1.09 mmol) and 15-crown-5 (0.2 mL) in dry dimethylformamide (3.5 mL) under an argon atmosphere at room temperature was treated with sodium hydride (0.055 g of 60% dispersion, 1.36 mmol) for 24h and then 2-chloroethyl methyl sulfide (0.145 mL, 1.46 mmol) was added dropwise. After another 24h, additional sodium hydride (0.55 g of 60% dispersion, 1.36 mmol) was added and, after 2.5h, the mixture was cooled and additional 2-chloroethyl methyl sulfide (0.145 mL, 1.46 mmol) was added dropwise; after 6d at room temperature, these additions were repeated. After 24h, water was added and the mixture was extracted with ethyl acetate. The extract was washed five times with water, was dried (sodium sulfate) and the solvent was removed *in vacuo*. The residue was washed with hexanes and was purified by flash chromatography, eluting with 2-3:1 ethyl acetate/hexanes, to provide an oil. Analysis Calc. for C₁₉H₂₇NO₃S·1/4 H₂O: C 64.47, H 7.83, N 3.94; found: C 64.40, H 7.81, N 4.20.

EXAMPLE 19

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

5 Inhalant Formulation

A compound of formula I, (1 µg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

<u>Tablets/Ingredients</u>	<u>Per Tablet</u>
1. Active ingredient (Cpd of Form. I)	40 mg
2. Corn Starch	20 mg
3. Alginic acid	20 mg
4. Sodium alginate	20 mg
5. Mg stearate	<u>1.3 mg</u> 2.3 mg

10 Procedure for tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No.4 in a suitable mixer/blender.

Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until
15 the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

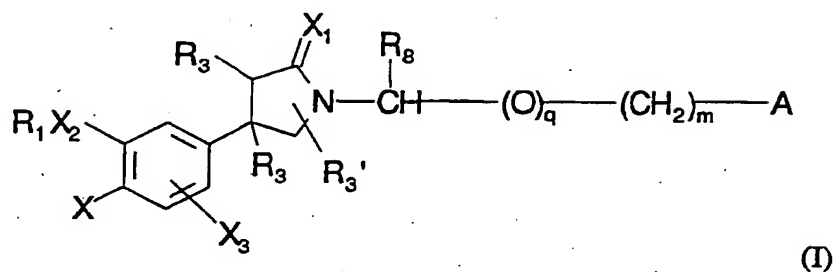
20 Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol
25 with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

CLAIMS:

1. A compound of the formula:



5

wherein:

- R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cycloalkyl unsubstituted or substituted by 1 to 3 methyl groups or an ethyl group; C_{4-6} cycloalkenyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl,
 10 $-(CR_{14}R_{14})_n C(O)O-(CR_{14}R_{14})_m R_{10}$, $-(CR_{14}R_{14})_n C(O)O-(CR_{14}R_{14})_r R_{11}$, $-(CR_{14}R_{14})_x OH$, $-(CR_{14}R_{14})_s O(CR_{14}R_{14})_m R_{10}$, $-(CR_{14}R_{14})_s O(CR_{14}R_{14})_r R_{11}$, $-(CR_{14}R_{14})_n (C(O)NR_{14})-(CR_{14}R_{14})_m R_{10}$, $(CR_{14}R_{14})_n (C(O)NR_{14})-(CR_{14}R_{14})_r R_{11}$, $-(CR_{14}R_{14})_y R_{11}$ or $-(CR_{14}R_{14})_z R_{10}$;

X_1 is O or S;

- 15 X_2 is O or NR_{14} ;

X_3 is hydrogen or X;

X is YR_2 , halogen, nitro, $NR_{14}R_{14}$, or formamide;

Y is O or $S(O)_m$;

- 20 R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 5 fluorines;

R_3 is independently hydrogen, halogen, CN, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, cyclopropyl unsubstituted or substituted by R_9 , OR_5 , $-CH_2OR_5$, $-NR_5R_{16}$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$, $-CH=CR_9R_9$, $-C\equiv CR_9$, or $-C(Z)H$;

- 25 R_3' is hydrogen, halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, cyclopropyl unsubstituted or substituted by R_9 , $-CN$, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or $-C(Z)H$;

- A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl) or (4 or 5-thiazolyl) all of which may be unsubstituted or substituted by one or more: Br, F, Cl, NR_5R_{16} , NR_6R_{16} ,
 30 NO_2 , $-COR_7$, $-S(O)_m R_{12}$, CN, OR_5 , $-OC(O)NR_5R_{16}$, (1- or 1-(R_5)-2-imidazolyl), 2-imidazolyl, $-C(NR_{16})NR_5R_{16}$, $-C(NR_5)SR_{12}$, $-OC(O)R_5$, $-C(NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen

form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR₁₂;

R₅ is independently hydrogen or C₁₋₄alkyl, unsubstituted or substituted by one to three fluorines;

5 R₆ is R₅, -C(O)R₅, -C(O)C(O)R₇, -C(O)NR₅R₁₆, -S(O)_mR₁₂, -C(NCN)S(R₁₂), -C(NCN)NR₅R₁₆, -C(NCN)R₁₂, -C(NR₁₆)R₁₂ or -C(NR₁₆)SR₁₂;

R₇ is OR₅, -NR₅R₁₆ or R₁₂C(NR₁₆)SR₁₂;

10 R₈ is hydrogen, C(O)R₇, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl-[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl) or (2-, 4-, or 5-imidazolidinyl), wherein each of the heterocyclic ring systems may be optionally substituted by one or more R₁₄ groups;

15 R₉ is hydrogen, F or R₁₂;

R₁₀ is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC₁₋₃alkyl, halo substituted aryloxyC₁₋₃alkyl, indanyl, indenyl, C₇₋₁₁ polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranlyl, 3-tetrahydrothienyl, (3- or 4-tetrahydropyranyl), C₃₋₆ cycloalkyl
20 or a C₄₋₆cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R₁₁ is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranlyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one
25 ethyl group;

R₁₂ is C₁₋₄alkyl unsubstituted or substituted by one to three fluorines;

R₁₄ is independently hydrogen or a C₁₋₂alkyl unsubstituted or substituted by fluorine;

30 R₁₅ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

R₁₆ is OR₅ or R₅;

35 Z is O, NR₁₂, NOR₅, NCN, C(-CN)₂, CR₅NO₂, CR₅C(O)OR₅, CR₅C(O)NR₅R₅, C(-CN)NO₂, C(-CN)C(O)OR₁₂ or C(-CN)C(O)NR₅R₅;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

x is an integer from 2 to 6;

y is an integer from 1 to 6;

5 z is an integer from 0 to 6;

or a pharmaceutically acceptable salt thereof;

provided that m is 2 when R₁₀ is OH in $-(\text{CR}_{14}\text{R}_{14})_n\text{-C(O)O-}$

$(\text{CR}_{14}\text{R}_{14})_m\text{R}_{10}$, $-(\text{CR}_{14}\text{R}_{14})_n(\text{C(O)NR}_{14})(\text{CR}_{14}\text{R}_{14})_m\text{R}_{10}$ or

10 $-\text{C(R}_{14}\text{R}_{14})_s\text{O(CR}_{14}\text{R}_{14})_m\text{R}_{10}$, and further provided that z is 2 to 6 when R₁₀ is OH in $-(\text{CR}_{14}\text{R}_{14})_z\text{R}_{10}$, and further provided that m is 1 or 2 when A is SR₁₂.

2. A compound of claim 1 wherein X₁ and X₂ are oxygen; A is an optionally substituted 2, 3 or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl; X is YR₂; Y is O; R₁ is CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl, phenyl, tetrahydrofur-3-yl, cyclopentenyl, -C₁₋₂alkyl optionally substituted by one or more fluorines, $-(\text{CH}_2)_n\text{C(O)-O-(CH}_2)_m\text{CH}_3$, $-(\text{CH}_2)_s\text{O(CH}_2)_m\text{-CH}_3$, $-(\text{CH}_2)_{2-4}\text{OH}$; R₂ is a C₁₋₂alkyl optionally substituted by one or more fluorines; one R₃ is hydrogen and the other R₃ is hydrogen, C≡CR₉, CN, C(Z)H, CH₂OH, CH₂F, CF₂H, or CF₃; Z is O or NOR₅; R_{3'} is hydrogen; and X₃ is hydrogen.

3. A compound of claim 1 wherein R₁ is C₁₋₄ alkyl substituted by 1 or more fluorines, CH₂-cyclopropyl, CH₂-cyclopentyl, cyclopentyl or cyclopentenyl; R₂ is methyl or fluoro substituted C₁₋₂ alkyl; R₃ is hydrogen, C≡CH or CN; and A is 2, 3 or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl, all of which may be unsubstituted or substituted by NR₅R₁₆ or NR₅C(O)R₅.

4. A compound of claim 1 wherein R₁ is cyclopentyl, CF₃, CH₂F, CHF₂, CF₂CHF₂, CH₂CF₃, CH₂CHF₂, CH₃, CH₂-cyclopentyl, CH₂-cyclopropyl or cyclopentenyl; R₂ is CH₃, CF₃, CHF₂, or CH₂CHF₂; one R₃ is hydrogen and the other R₃ is hydrogen, C≡CH or CN and is in the 4-position.

5. A compound of claim 1 selected from the group consisting of:

1-(2-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

1-(3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

1-(4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

35 1-[2-(4-morpholinyl)ethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

1-(2-imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(S)-(-)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(S)-(-)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

5 (R)-(+)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-(+)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

10 (S)-(-)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-(+)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

S-(-)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone; and

15 R-(+)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone; and

4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-methylthioethyl)-2-pyrrolidinone.

20 6. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

8. A method for the inhibition of the production of tumor necrosis factor (TNF) in a mammal in need thereof, including humans, which comprises administering to the mammal in need thereof, an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

25 9. A method of treatment of allergic and inflammatory diseases which comprise administering to a subject in need thereof, an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/08611

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5	C 07 D 401/06	C 07 D 403/06	C 07 D 409/06
C 07 D 413/06	A 61 K 31/40	A 61 K 31/38	A 61 K 31/41

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System

Classification Symbols

Int.Cl.5

C 07 D

A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category¹⁰

Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²

Relevant to Claim No.¹³

X	US,A,4476311 (THE PURDUE FREDERICK COMPANY) October 1984 see column 1, line 32 - column 2, line 25 the entire document *	1-9
Y	---	1-8
Y	WORLD PATENTS INDEX Week 7636, Derwent Publications Ltd., London, GB; AN 76-67577X & JP,A,51 082 258 (YOSHITOMI PHARM. IND. KK) 20 July 1976 see abstract ---	1-8
A	EP,A,0114033 (CIBA-GEIGY AG) claims * see page 6, line 28 - page 7, line 14 ---	1-8
A	EP,A,0350437 (SCHERING AG) claims * ---	1-8
	-/-	

¹⁰ Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

21-12-1992

Date of Mailing of this International Search Report

28. 01. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Natalie Weinberg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0439766 (ARZNEIMITTELWERK DRESDEN) August 1991 claims *	1-8
A	FR,A,2100946 (UCB) claims *	1-8
A	EP,A,0270093 (TANABE SEIYAKU CO., LTD.) 1988 see claim 4	1-8
A	CHEMICAL ABSTRACTS, vol. 101, no. 25, 17 December 1984, Columbus, Ohio, US; abstract no. 230442, M. KOBAYASHI ET AL.: 'Studies on the synthesis of antiulcer agents. I. Synthesis and antiulcer activity of imide derivatives' page 763 ; see abstract & Yakugaku Zasshi 104 (6) 652-8 (1984)	1-3
A	CHEMICAL ABSTRACTS, vol. 114, no. 11, 18 March 1991, Columbus, Ohio, US; abstract no. 101601, T. A. VORONINA ET AL.: 'Synthesis and pharmacological properties of amidine analogs of pyracetam' page 710 ; see abstract & Khim.-Farm. Zh. 24 (11) 26-9 (1990)	1-3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/08611

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8,9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9208611
SA 65706

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/01/93. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4476311	09-10-84	US-A- 4639529 US-A- 4731457	27-01-87 15-03-88
EP-A- 0114033	25-07-84	AU-B- 565914 AU-A- 2270483 CA-A- 1208649 DE-A- 3378208 JP-A- 59118748 US-A- 4839379	01-10-87 28-06-84 29-07-86 17-11-88 09-07-84 13-06-89
EP-A- 0350437	10-01-90	DE-A- 3823299 JP-A- 2085250 US-A- 5064854	11-01-90 26-03-90 12-11-91
EP-A- 0439766	07-08-91	None	
FR-A- 2100946	24-03-72	AT-A, B 310150 AT-A, B 304530 AU-B- 461836 AU-A- 3157571 BE-A- 770308 CA-A- 954870 CH-A- 537921 CH-A- 538474 DE-A, C 2136571 GB-A- 1350582 NL-A- 7109930 SE-B- 379347 US-A- 3956314	15-08-73 15-12-72 05-06-75 25-01-73 24-01-72 17-09-74 31-07-73 15-08-73 27-01-72 18-04-74 26-01-72 06-10-75 11-05-76
EP-A- 0270093	08-06-88	AU-A- 8181187 FR-A- 2607809 JP-A- 63264458 US-A- 4839360	09-06-88 10-06-88 01-11-88 13-06-89

EPO FORM 1017

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)